CHAPTER 76

LUNG TRANSPLANTATION

İlhan İNCİ [1]

INTRODUCTION

Lung transplantation (LTX) is an established therapeutic option for end-stage lung disease in selected patients. During the last 40 years more than 40000 transplantations have been performed worldwide (1). Emphysema, pulmonary fibrosis, cystic fibrosis and primary pulmonary hypertension are the most common indications. This type of surgical treatment is increasingly successful with better early and late survival rates. However, LTX is still hampered by persisting problems such as donor organ shortage, primary graft dysfunction, late graft dysfunction, and morbidity related to long-term immunosuppression. This review will address the current clinical LTX and future directions.

HISTORY

Vlademir Demikhov, Russian physiologist and surgeon performed the first lung, heart and heart-lung transplantation in dogs. These remarkable studies demonstrated the technical feasibility of intrathoracic organ replacement (2).

Henry Metras, in 1949 described important technical concepts including preservation of left atrial cuff for the pulmonary venous anastomosis. He proposed the preservation of bronchial arterial system to prevent airway anastomotic problems. Unfortunately this technique never gained widespread popularity (3).

In 1963, James Hardy performed the first human lung transplantation (4). The recipient survived the operation for 18 days and died of renal failure. This first attempt of LTX precipitated a flurry of activity in experimental and clinical LTX. However, the results were very disappointing. By 1980, almost 20 years after the first attempt, a total of 38 patients were transplanted of which 2 survived 6 and 10 months. Most of the patients who survived 10 days or more died of bronchial anastomotic complications.

In 1981, Bruce Reitz and Norman Shumway at Stanford University performed the first successful heart and LTX. This important step opened the way for contemporary clinical LTX results (5).

In 1983 Dr. Cooper and his team in Toronto General Hospital performed the first successful single LTX for IPF (6). This was the first long term survival after LTX. The recipient survived 7 years. By the 1990, Starnes at Stanford performed the first living related lobar LTX (7).

In 1992, Prof Weder in Zurich was performing successfully the first LTX in Switzerland. That was single right LTX in an emphysema patient.

INDICATIONS AND RECIPIENT SELECTION

The indications for LTX have extended over time and include a diverse spectrum of pulmo-

[1] Prof., University of Zurich, University Hospital, Department of Thoracic Surgery, Zurich Switzerland ilhan.inci@usz.ch

transplant setting. Decellularized lung, which can maintain a near intact extracellular matrix (ECM) and the complex microarchitecture of the lung, has been shown to be an ideal scaffold for reseeding with cells (92). Thus, recellularization based lung regeneration may prove to be an effective clinical therapy for future treatment of lung diseases (92). Recently, transplantation of bioengineered rat lungs recellularized with endothelial and adipose-derived stromal cells has been performed (93).

However, there are still many issues that remain to be resolved before such bioengineered lungs become available for clinical use. Issues still to be resolved include: the ideal decellularization method, the ideal duration for whole lung recellularization and the minimum number and types of necessary cells (92,93).

CONCLUSION

The additional improvement in post-transplant survival of lung transplant recipients in the recent era at our center is most likely due to a number of factors: Better surgical techniques, organ preservation and intensive-care management likely played a role. In addition, careful post-transplant long-term management by transplant pulmonologists, including rigorous treatment of airway infections, sinus surgery and routine nasal care (CF recipients), long-term therapy with macrolide antibiotics for chronic lung allograft dysfunction (CLAD), and extracorporeal photopheresis in selected recipients with CLAD and recurrent acute allograft rejection might have contributed to improved outcomes at our center as well (94,95).

The two main problems are limited organ supply and failure to ensure long-term allograft function with the current immunosuppression strategies. Increased use of DCD donors, utilization of EVLP to assess and recondition marginal donor organs, and advances in tissue engineering research could overcome at least the limited supply of eligible donor lungs for lung transplantation.

There are still many issues that remain to be resolved before such bioengineered lungs become available for clinical use. Issues still to be resolved include: the ideal decellularization method, the ideal duration for whole lung recellularization and the minimum number and types of necessary cells (92,93).

REFERENCES

1. Chambers DC, Yusen RD, Cherikh WS, et al; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017 Oct;36(10):1047-1059
2. Demikhov VP. Transplantation of the heart, lungs and other organs. Eksp Khir Anesteziol 1969;14:3-8.
3. Metras H. Note preliminaire sur greffe totale du poumon chez le chien. Comp Renal Acad Sci 1950;231:1176-7
4. Hardy JD, Webb WR, Dalton ML Jr, et al. Lung homotransplantation in man. JAMA 1963;186:1065-74.
5. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE. 1982. Heart– lung transplantation: Successful therapy for patients with pulmonary vascular disease. N Engl J Med 306: 557 – 564.
6. Toronto Lung Transplant Group: unilateral lung transplantation for pulmonary fbrosis. N Engl J Med 1986;314:1140-5.
7. Starnes VA, Lewiston NJ, Luikart H, et al. Current trends in lung transplantation: lobar transplantation and expanded use of single lungs. J Thorac Cardiovasc Surg 1992;104:1060-5; discussion 1065-6.
8. Weill D, Benden C, Corris PA, et al. consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015 Jan;34(1):1-15.)
9. Orens JB, Boehler A, de Perrot M, et al. A review of lung transplant donor acceptability criteria. J Heart Lung Transplant. 2003;22(11):1183-200.
10. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. Am J Respir Crit Care Med 1999;160:265–71.
11. Straznicka M, Follette DM, Eisner MD, et al. Aggressive management of lung donors classified as unacceptable: excellent recipient survival one year after transplantation. J Thorac Cardiovasc Surg 2002;124:250–8.
12. Pierre AF, Sekine Y, Hutcheon MA, et al. Marginal donor lungs: a reassessment. J Thorac Cardiovasc Surg 2002;123:421–8.
13. Lardinois D, Banysch M, Korom S, et al. Extended donor lungs: eleven years experience in a consecutive series. Eur J Cardiothorac Surg. 2005 May;27(5):762-7.

14. Yeung JC, Keshavjee S. Overview of clinical lung transplantation. Cold Spring Harb Perspect Med 2014;4:a015628
15. Weder W, Inci I, Korom S, et al. Airway complications after lung transplantation: risk factors, prevention and outcome. Eur J Cardiothorac Surg. 2009; 35: 293-298.
16. Inci I, Weder W. Airway complications after lung transplantation can be avoided without bronchial artery revascularization. Curr Opin Organ Transplant. 2010; 15(5):578-81.
17. Schuurmans MM, Benden C, Inci I. Practical approach to early postoperative management of lung transplant recipients. Swiss Med Wkly 2013;143:w13773.
18. Korom S, Boehler A, Weder W. Immunosuppressive therapy in lung transplantation: state of the art. Eur J Cardiothorac Surg. 2009;35(6):1045–55.
19. Inci-Book Chapter Surgical Complications
20. Date H, Trulock EP, Arcidi JM, et al. Improved airway healing after lung transplantation. An analysis of 348 bronchial anastomoses. J Thorac Cardiovasc Surg. 1995;110(5):1424-32.
21. Wildevuur C.R.H., Benfield J.R. A review of 23 human lung transplants by 20 surgeons. Ann Thorac Surg 1970;9:489-515.
22. Ruttmann E, Ulmer H, Marchese M, et al. Evaluation of factors damaging the bronchial wall in lung transplantation.J Heart Lung Transplant. 2005;24(3):275-81.
23. Schroder C, Scholl F, Daon E, et al. A modified bronchial anastomosis technique for lung transplantation. Ann Thorac Surg. 2003 ;75(6):1697-704.
24. Alvarez A, Algar J, Santos F, et al. Airway complications after lung transplantation: a review of 151 anastomoses. Eur J Cardiothorac Surg. 2001;19(4):381-7.
25. Choong CK, Sweet SC, Zoole JB, et al. Bronchial airway anastomotic complications after pediatric lung transplantation: incidence, cause, management, and outcome. J Thorac Cardiovasc Surg. 2006;131(1):198-203.
26. Herrera JM, McNeil KD, Higgins RS, et al. Airway complications after lung transplantation: treatment and long-term outcome. Ann Thorac Surg. 2001;71:989-93.
27. Aigner C, Jaksch P, Seebacher G, et al. Single running suture--the new standard technique for bronchial anastomoses in lung transplantation. Eur J Cardiothorac Surg. 2003 ;23(4):488-93.
28. Murthy SC, Blackstone EH, Gildea TR, et al. Impact of anastomotic airway complications after lung transplantation. Ann Thorac Surg. 2007 Aug;84(2):401-9.
29. Van De Wauwer C, Van Raemdonck D, Verleden GM, et al. Risk factors for airway complications within the first year after lung transplantation. Eur J Cardiothorac Surg. 2007 ;31(4):703-1.
30. Takao M., Katayama Y., Onoda K., et al. Significance of bronchial mucosal blood flow for the monitoring of acute rejection in lung transplantation. J Heart Lung Transplant 1991;10:956-967.
31. Schmid RA, Boehler A, Speich R, et al. Bronchial anastomotic complications following lung transplantation: still a major cause of morbidity? Eur Respir J. 1997;10(12):2872-5.
32. Lee JC, Christie JD. Primary graft dysfunction. Proc Am Thorac Soc. 2009 Jan 15;6(1):39-46.
33. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT working group on primary lung graft dysfunction: Part II. Definition. *J Heart Lung Transplant* 2005;24:1454–1459.
34. 50.Christie JD, Bavaria JE, Palevsky HI, Litzky L, Blumenthal NP, Kaiser LR, Kotloff RM. Primary graft failure following lung transplantation. *Chest* 1998;114:51–60.
35. King RC, Binns OA, Rodriguez F, Kanithanon RC, Daniel TM, Spotnitz WD, Tribble CG, Kron IL. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. *Ann Thorac Surg* 2000;69:1681–1685.
36. Christie JD, Kotloff RM, Pochettino A, Arcasoy SM, Rosengard BR, Landis JR, Kimmel SE. Clinical risk factors for primary graft failure following lung transplantation. *Chest* 2003;124:1232–1241.
37. Arcasoy SM, Kotloff RM. Lung transplantation. *N Engl J Med* 1999;340:1081–1091.
38. Christie JD, Sager JS, Kimmel SE, Ahya VN, Gaughan C, Blumenthal NP, Kotloff RM. Impact of primary graft failure on outcomes following lung transplantation. *Chest* 2005;127:161–165.
39. Arcasoy SM, Fisher A, Hachem RR, Scavuzzo M, Ware LB. Report of the ISHLT working group on primary lung graft dysfunction: Part V. Predictors and outcomes. *J Heart Lung Transplant* 2005;24:1483–1488.
40. Christie JD, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, DeMissie E, Kimmel SE. The effect of primary graft dysfunction on survival after lung transplantation. *Am J Respir Crit Care Med* 2005;171:1312–1316.
41. Christie JD, Van Raemdonck D, de Perrot M, Barr M, Keshavjee S, Arcasoy S, Orens J. Report of the ISHLT working group on primary lung graft dysfunction: Part I. Introduction and methods. *J Heart Lung Transplant* 2005;24:1451–1453.
42. Miotla JM, Jeffery PK, Hellewell PG. Platelet-activating factor plays a pivotal role in the induction of experimental lung injury. *Am J Respir Cell Mol Biol* 1998;18:197–204.
43. Serrick C, Adoumie R, Giaid A, Shennib H. The early release of interleukin-2, tumor necrosis factor-alpha and interferon-gamma after ischemia reperfusion injury in the lung allograft. *Transplantation* 1994;58:1158–1162.
44. Moreno I, Vicente R, Ramos F, Vicente JL, Barbera M. Determination of interleukin-6 in lung transplantation: association with primary graft dysfunction. *Transplant Proc* 2007;39:2425–2426.
45. de Perrot M, Bonser RS, Dark J, Kelly RF, McGiffin D, Menza R, Pajaro O, Schueler S, Verleden GM. Report of the ISHLT working group on primary lung graft dysfunction: Part III. Donor-related risk factors and markers. *J Heart Lung Transplant* 2005;24:1460–1467.
46. Barr ML, Kawut SM, Whelan TP, Girgis R, Bottcher H, Sonett J, Vigneswaran W, Follette DM, Corris PA. Report of the ISHLT working group on primary lung graft dysfunction: Part IV. Recipient-related risk factors and markers. *J Heart Lung Transplant* 2005;24:1468–1482.

47. Cassivi SD, Meyers BF, Battafarano RJ, Guthrie TJ, Trulock EP, Lynch JP, Cooper JD, Patterson GA. Thirteen-year experience in lung transplantation for emphysema. *Ann Thorac Surg* 2002;74:1663–1669. (discussion 1669–1670).
48. Szeto WY, Kreisel D, Karakousis GC, Pochettino A, Sterman DH, Kotloff RM, Arcasoy SM, Zisman DA, Blumenthal NP, Gallop RJ, *et al.* Cardiopulmonary bypass for bilateral sequential lung transplantation in patients with chronic obstructive pulmonary disease without adverse effect on lung function or clinical outcome. *J Thorac Cardiovasc Surg* 2002;124:241–249.
49. Shargall Y, Guenther G, Ahya VN, Ardehali A, Singhal A, Keshavjee S. Report of the ISHLT working group on primary lung graft dysfunction: Part VI. Treatment. *J Heart Lung Transplant* 2005;24:1489–1500.
50. Adatia I, Lillehei C, Arnold JH, Thompson JE, Palazzo R, Fackler JC, Wessel DL. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. *Ann Thorac Surg* 1994;57:1311–1318.
51. Date H, Triantafillou AN, Trulock EP, Pohl MS, Cooper JD, Patterson GA. Inhaled nitric oxide reduces human lung allograft dysfunction. *J Thorac Cardiovasc Surg* 1996;111:913–919.
52. Macdonald P, Mundy J, Rogers P, Harrison G, Branch J, Glanville A, Keogh A, Spratt P. Successful treatment of life-threatening acute reperfusion injury after lung transplantation with inhaled nitric oxide. *J Thorac Cardiovasc Surg* 1995;110:861–863.
53. Fiser SM, Kron IL, McLendon Long S, Kaza AK, Kern JA, Tribble CG. Early intervention after severe oxygenation index elevation improves survival following lung transplantation. *J Heart Lung Transplant* 2001;20:631–636.
54. Meyers BF, Sundt TM III, Henry S, Trulock EP, Guthrie T, Cooper JD, Patterson GA. Selective use of extracorporeal membrane oxygenation is warranted after lung transplantation. *J Thorac Cardiovasc Surg* 2000;120:20–26.
55. Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone EH, Cosgrove DM III. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. *J Thorac Cardiovasc Surg* 2001;122:92–102.
56. Kermeen FD, McNeil KD, Fraser JF, McCarthy J, Ziegenfuss MD, Mullany D, Dunning J, Hopkins PM. Resolution of severe ischemia-reperfusion injury post-lung transplantation after administration of endobronchial surfactant. *J Heart Lung Transplant* 2007;26:850–856.
57. Amital A, Shitrit D, Raviv Y, et al. The use of surfactant in lung transplantation. Transplantation. 2008 Dec 15;86(11):1554-9.
58. Inci I, Zhai W, Arni S, Hillinger S, Vogt P, Weder W. N-acetylcysteine attenuates lung ischemia-reperfusion injury after lung transplantation. *Ann Thorac Surg* 2007;84:240–246.
59. Chamogeorgakis TP, Kostopanagiotou GG, Kalimeris CA, Kabouroglou GI, Kourtesis AN, Routsi CI, Dima CC, Toumpoulis IK. Effect of n-acetyl-l-cysteine on lung ischaemia reperfusion injury in a porcine experimental model. *ANZ J Surg* 2008;78:72–77.
60. Wolf PS, Merry HE, Farivar AS, McCourtie AS, Mulligan MS. Stress-activated protein kinase inhibition to ameliorate lung ischemia reperfusion injury. *J Thorac Cardiovasc Surg* 2008;135:656–665.
61. Christie JD, Edwards LB, Kucheryavaya AY, et al; International Society of Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant. 2012 ;31(10):1073-86.
62. Aigner C, Wisser W, Taghavi S, et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. Eur J Cardiothorac Surg. 2007;31(3):468-73.
63. Hoopes CW, Kukreja J, Golden J, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013;145:862-68.
64. Barr ML, Schenkel FA, Cohen RG, et al. Recipient and donor outcomes in living related and unrelated lobar transplantation. Transplant Proc 1998; 30: 2261-2263.
65. Aigner C, Jaksch P, Taghavi S, et al. Donor total lung capacity predicts recipient total lung capacity after size-reduced lung transplantation. J Heart Lung Transplant 2005; 24: 2098-2102.
66. Aigner C, Winkler G, Jaksch P, et al. Size-reduced lung transplantation: an advanced operative strategy to alleviate donor organ shortage. Transplant Proc 2004; 36: 2801-2805.
67. Shigemura N, Bermudez C, Hattler BG, et al. Impact of graft volume reduction for oversized grafts after lung transplantation on outcome in recipients with end-stage restrictive pulmonary diseases. J Heart Lung Transplant 2009; 28: 130-134.
68. Artemiou O, Wieselthaler G, Zuckermann A, et al. Downsizing of the donor lung: peripheral segmental resections and lobar transplantation. Transplant Proc 1997; 29: 2899-2900.
69. Aigner C, Mazhar S, Jaksch P, et al. Lobar transplantation, split lung transplantation and peripheral segmental resection--reliable procedures for downsizing donor lungs. Eur J Cardiothorac Surg 2004; 25: 179-183.
70. Santos F, Lama R, Alvarez A, et al. Pulmonary tailoring and lobar transplantation to overcome size disparities in lung transplantation. Transplant Proc 2005; 37: 1526-1529.
71. Inci I, Irani S, Kestenholz P, et al. Donor predicted post-operative forced expiratory volume in one second predicts recipients' best forced expiratory volume in one second following size-reduced lung transplantation. Eur J Cardiothorac Surg. 2011:39:115-9.
72. Benden C, Inci I, Weder W, Boehler A. Size-reduced lung transplantation in children--an option worth to consider! Pediatr Transplant. 2010;14(4):529-33..
73. Inci I, Schuurmans, Kestenholz P, et al. Long-term outcomes of bilateral lobar lung transplantation. Eur J Cardiothorac Surg. 2012.
74. Inci I. Donors after cardiocirculatory death and lung transplantation. J Thorac Dis 2017;9(8):2660-2669.

75. Cypel M, Levvey B, Van Raemdonck D, et al. International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report. J Heart Lung Transplant 2015;34:1278-82.
76. Cypel M, Sato M, Yildirim E, et al. Initial experience with lung donation after cardiocirculatory death in Canada. J Heart Lung Transplant. 2009;28:753-8.
77. Levvey BJ, Harkess M, Hopkins P, et al. Excellent Clinical Outcomes from a National Donation-After-Determination-of-Cardiac-Death Lung Transplant Collaborative. Am J Transplant 2012;12: 2406-13.
78. Snell G.I., B.J. Levvey , T. Oto et al., Early lung transplantation success utilizing controlled donation after cardiac death donors, Am J Transplant 2008;8:1282–1289.
79. De Vleeschauwer S, Van Raemdonck D, Vanaudenaerde B, et al. Early outcome after lung transplantation from non-heart-beating donors is comparable to heart-beating donors. J Heart Lung Transplant 2009;28:380-7.
80. Steen S, Söberg T, Pierre L, et al. Transplantation of lungs from a non-hear-beating donor. Lancet 2001;357:825-29.
81. Krueger T, Berutto C, Aubert JD: Challenges in lung transplantation. Review article. Swiss Med Wkly. 2011;141:w13292.
82. Wierup P, Haraldsson A, Nilsson F, et al. Ex vivo evaluation of nonacceptable donor lungs. Ann Thorac Surg. 2006;81:460-6.
83. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg. 2012;144:1200-6.
84. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med. 2011;14;364:1431-40.
85. Aigner C, Slama A, Hötzenecker K, et al. Clinical ex vivo lung perfusion--pushing the limits. Am J Transplant. 2012;12:1839-47.
86. Inci I, Arni S, Acevedo C, et al. Surfactant alterations following donation after cardiac death donor lungs. Transpl Int. 2011;24(1):78-84.
87. Inci I, Ampollini L, Arni S, et al. Ex vivo reconditioning of marginal donor lungs injured by acid aspiration. J Heart Lung Transplant. 2008;27(11):1229-36.
88. Inci I, Arni S, Inci D, et al. Impact of topical cooling solution and prediction of pulmonary graft viability from non-heart-beating donors. J Heart Lung Transplant. 2008 ;27(9):1016-22.
89. Inci I, Zhai W, Arni S, et al. Fibrinolytic treatment improves the quality of lungs retrieved from non-heart-beating donors. J Heart Lung Transplant. 2007;26:1054-60.
90. Inci I, Yamada Y, Hillinger S, et al. Successful lung transplantation after donor lung reconditioning with urokinase in an ex-vivo lung perfusion system. Ann Thorac Surg 2014;98:1837-8.
91. Ott HC, Clippinger B, Conrad C, et al. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med. 2010;16(8):927-33.
92. Tsuchiya T, Sivarapatna A, Rocco K, Nanashima A, Nagayasu T, Niklason LE. Future prospects for tissue engineered lung transplantation: decellularization and recellularization-based whole lung regeneration. Organogenesis. 2014 Apr-Jun;10(2):196-207.
93. Doi R, Tsuchiya T, Mitsutake N, et al. Transplantation of bioengineered rat lungs recellularized with endothelial and adipose-derived stromal cells. Sci Rep. 2017 Aug 16;7(1):8447.
94. Hofer M, Benden C, Inci I, et al. True survival benefit of lung transplantation for cystic fibrosis patients: the Zurich experience. J Heart Lung Transplant 2009; 28:334-9.
95. Inci I, Stanimirov O, Benden C, et al. Lung transplantation for cystic fibrosis: a single center experience of 100 consecutive cases. Eur J Cardiothorac Surg. 2012:41:435-40.